

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number  
**WO 03/103675 A2**

(51) International Patent Classification<sup>7</sup>: **A61K 31/522**,  
31/675, A61P 9/00, 11/00

(21) International Application Number: PCT/US03/17964

(22) International Filing Date: 6 June 2003 (06.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/386,769 6 June 2002 (06.06.2002) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,  
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,  
UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— without international search report and to be republished  
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.



**WO 03/103675 A2**

(54) Title: COMBINATION TREATMENTS FOR PURINOCEPTOR-RELATED DISORDERS

(57) Abstract: The present invention provides methods of preventing and treating purinoceptor-related disorders comprising con-  
currently administering an A1 adenosine receptor antagonist or a P<sub>2x</sub> purinoceptor antagonist with an at least one additional active  
agent effective to treat purinoceptor-related disorders. The present invention also provides pharmaceutical formulations suitable for  
preventing and treating purinoceptor-related disorders.

## COMBINATION TREATMENTS FOR PURINOCEPTOR-RELATED DISORDERS

5

### Cross Reference to Related Applications

This application claims the benefit of U.S. Provisional Application Serial No. 60/386,769 filed June 6, 2002, the disclosure of which is incorporated herein by reference in its entirety.

### Field of the Invention

This invention relates to methods of use for A<sub>1</sub> adenosine receptor antagonists or P<sub>2x</sub> purinoceptor antagonists in combination with other treatments for prevention and treatment of purinoceptor-related disorders. The invention also relates to therapeutically useful pharmaceutical formulations.

### Background of the Invention

According to the National Heart, Lung, and Blood Institute (NHLBI) from the National Institutes of Health (NIH) and the World Health Organization (WHO), asthma is defined as a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness, airflow limitation which is partially reversible, and respiratory symptoms of wheezing, breathlessness, cough, and chest tightness (National Institutes of Health/NHLBI 1995. Global strategy for asthma management and prevention NHLBI/WHO workshop report March 1993. NIH Publication No. 95-3659. Bethesda MD: US Dept of Health and National Heart, Lung, and Blood Institute).

In the U.S., "asthma is one of the most common and costly diseases. More than 5% of the U.S. population has asthma and the numbers are growing" (National Center for Environment Health, Centers for Disease Control and Prevention, Asthma prevention program at-a-glance, (1999)). The mortality rate for asthma is increasing, especially in urban areas (National Center for Environment Health, Centers for Disease Control and Prevention, 1999; Addington WW, Weiss KB. Chicago's response to the public health challenge of urban asthma. *Chest* 116:132S-134S (1999)).

5           Currently, the treatment of asthma is avoidance of allergens and use of mast cell stabilizers, beta-2 agonists, xanthines (e.g. theophylline), anti-histamines, steroids, and leukotriene antagonists. Many of the current treatments, e.g. steroids and beta-2 agonists, may produce serious side effects, and as in the case of leukotriene antagonists, are only modestly effective.

10           Adenosine produces bronchoconstriction in asthmatics when administered as an inhalational challenge, and currently adenosine receptors (ARs) are considered potential therapeutic targets for drug development in asthma, both as "acute rescue" drugs and preventive, maintenance drugs. A respiratory antisense oligonucleotide (RASON) to the human A<sub>1</sub> AR as an inhalational treatment for the prevention of  
15 human asthma is currently in clinical trials. Moreover, bamiphylline, a selective A<sub>1</sub> AR antagonist for the human A<sub>1</sub> AR, is used to treat asthma in Europe (Abbraccio MP and Cattabeni F. Selective activity of bamiphylline on adenosine A<sub>1</sub> – receptors in rat brain. *Pharmacol Res* 19:537-545 (1987)).

          Two large families of purinergic receptors have been characterized as P<sub>1</sub>  
20 (adenosine-sensitive) and P<sub>2</sub> (adenosine triphosphate, ATP- sensitive) purinoceptors. Those in the P<sub>1</sub> class have been further divided into four subtypes - A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and A<sub>3</sub> - based upon pharmacological profile such as binding to selective ligands, signal transduction mechanisms, and molecular sequences. P<sub>1</sub> AR subtypes A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and A<sub>3</sub> have been cloned in humans, and are coupled via G proteins to a number of  
25 intracellular signal transduction pathways, and are expressed in the lung (Marquardt DL. Adenosine. In Asthma, PJ Barnes, MM Grunstein, AR Leff, AJ Woolcock (eds), pp 585-591, Lippincott-Raven Publishers, Philadelphia, PA, 1997).

          Activation of A<sub>1</sub> ARs produces slowing of the heart, depression of heart contractility, bronchoconstriction, renal and pulmonary vasoconstriction,  
30 proinflammatory cellular effects, sleep induction, and antinociception (Ely SW and Berne RM: Protective effects of adenosine in myocardial ischemia. *Circulation* 85:893-904 (1992); Murray RD and Churchill PC: Effects of adenosine receptor agonists in the isolated perfused rat kidney. *Am J Physiol* 247:H343-H348 (1984); Neely CF, Haile DM, Cahill BE, Kadowitz PJ: Adenosine and adenosine 5'-  
35 triphosphate produce vasoconstriction in the feline pulmonary vascular bed by different mechanisms. *J Pharmacol Exp Ther* 258:753-761 (1991); Ali S, Mustafa SJ, Metzger WJ: Adenosine-induced bronchoconstriction and contraction of airway

- 5 smooth muscle from allergic rabbits with late-phase airway obstruction: evidence for an inducible adenosine A<sub>1</sub> receptor. *J Pharmacol Exp Ther* 268:1328-1334 (1993)).

The P<sub>2</sub> subclass of receptors refers to the receptors sensitive to adenosine triphosphate (ATP) and adenosine diphosphate (ADP). Previously, the P<sub>2</sub> receptors have been classified as P<sub>2x</sub> and P<sub>2y</sub> (Abbrachio MP and Burnstock G. Purinoceptors: are there families of P<sub>2x</sub> and P<sub>2y</sub> purinoceptors? *Pharmac Ther* 64:445-475 (1994)).  
10 Activation of P<sub>2x</sub> purinoceptors produces vasoconstriction, platelet aggregation, contraction of the urinary bladder and colon, nociception, and release of mediators from macrophages which are important in the pathophysiology of septic shock (Günter Lambrecht. Agonists and antagonists acting at P<sub>2x</sub> receptors: selectivity profiles and functional implications. *Naunyn-Schmiedeberg's Arch Pharmacol* 362: 34-350 (2000)). Moreover, activation of P<sub>2x</sub> purinoceptors on immune cells produces cell death by apoptosis (Burnstock G, Overview of P<sub>2</sub> receptors: possible functions in immune cells. *Drug Devel Res* 53:53-59 (2001)). However, the role of ARs in the pathophysiology and pathogenesis of asthma— hyperreactivity of human airways, the  
15 inflammatory response to allergens, airway edema, and the development of airway structural remodeling— seen in human allergic asthma is limited.

Many reports suggest that adenosine produces bronchoconstriction in humans by inducing the release of histamine and newly generated mediators from mast cells (Holgate ST. Experimental models of asthma. *Clin Exp Allergy* 29:82-86 (1999);  
25 Barnes PJ, Chung KF, Page CP. Inflammatory mediators of asthma: an update. *Pharmacol Rev* 50:515-596 (1998); Mundell SJ, Olah ME, Panettieri, Jr. RA, Benovic JL, Penn RB. Regulation of G protein-coupled receptor-adenylyl cyclase responsiveness in human airway smooth muscle by exogenous and autocrine adenosine. *Am J Respir Cell Mol Biol* 24:155-163 (2001); and Fozard JR and  
30 Hannon JP. Species differences in adenosine receptor-mediated bronchoconstrictor responses. *Clin Exp Allergy* 30:1213-1220 (2000)). In addition to mast cells, ARs are present on a number of other cell types which play important roles in the development of acute and chronic asthma, including bronchial smooth muscle cells, neutrophils, eosinophils, basophils, lymphocytes, monocytes and macrophages, platelets,  
35 endothelial cells, and fibroblasts. However their role in modulating immune and inflammatory responses in acute and chronic human asthma is unclear.

- 5           A<sub>1</sub>, A<sub>2a</sub>, and A<sub>3</sub> ARs have been identified in human monocytes and  
macrophages (Sajjadi FG, Takabayashi K, Foster AC, Domingo RC, Firestein GS.  
Inhibition of TNF-alpha expression by adenosine: role of A<sub>3</sub> adenosine receptors. *J*  
*Immunol*; 156:3435-3442 (1996); Eppell BA, Newell AM, Brown EJ. Adenosine  
receptors are expressed during differentiation of monocytes to macrophages in vitro.  
10   Implications for regulation of phagocytosis. *J Immunol* 143:4141-4145 (1989);  
Salmon JE, Brogle N, Brownlie C, Edberg JC, Kimberly RP, Chen BX, Erlanger BF.  
Human mononuclear phagocytes express adenosine A<sub>1</sub> receptors. A novel  
mechanism for differential regulation of Fc gamma receptor function. *J Immunol*  
151:2775-2785 (1993)). As a result of these findings, A<sub>2</sub> AR agonists have been  
15   implicated in the treatment of inflammatory diseases. See U.S. Patent No. 6,232,297  
to Linden et al. In human platelets and lung fibroblasts, A<sub>1</sub> and A<sub>2a</sub> ARs have been  
identified and inhibit and stimulate adenylate cyclase, respectively (Dionisotti S,  
Ferrara S, Molta C, Zocchi C, Ongini E. Labeling of A<sub>2a</sub> adenosine receptors in  
human platelets by use of the new nonxanthine antagonist radioligand [3H]  
20   SCH58261. *J Pharmacol Exp Ther* 278:1209-1214 (1996); Gurden MF, Coates J, Ellis  
F, Evans B, Foster M, Hornby E, Kennedy I, Martin DP, Strong P, Vardey CJ.  
Functional characterization of three adenosine receptor types. *Br J Pharmacol*  
109:693-698 (1993); Ahmed AH, Jacobson KA, Kim J, Heppel LA. Presence of both  
A<sub>1</sub> and A<sub>2a</sub> adenosine receptors in human cells and their interactions. *Biochem*  
25   *Biophys Res Commun* 208:871-878 (1995)).

- A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and A<sub>3</sub> ARs have also been identified in human endothelial cells.  
In human coronary artery endothelial cells, activation of both A<sub>2a</sub> and A<sub>2b</sub> ARs  
stimulates adenylate cyclase (Olanrewaju HA, Qin W, Feoktistov I, Scemama JL,  
Mustafa SJ. Adenosine A<sub>2a</sub> and A<sub>2b</sub> receptors in cultured human and porcine  
30   coronary artery endothelial cells. *Am J Physiol Heart Circ Physiol* 279:H650-H656  
(2000)). In human umbilical vein endothelial cells, activation of A<sub>1</sub> ARs stimulates  
and activation of A<sub>2</sub> and A<sub>3</sub> ARs inhibits stimulant-induced tissue factor expression,  
respectively (Deguchi H, Takeya H, Urano H, Gabazza EC, Zhou H, Suzuki K.  
Adenosine regulates tissue factor expression on endothelial cells. *Thromb Res* 91:57-  
35   64 (1998)). In human pulmonary artery endothelial cells, activation of A<sub>1</sub> ARs  
induces the release of thromboxane and IL-6, both of which increase vascular  
permeability (Neely CF and Batra VK. Lipopolysaccharide binds to and activates A<sub>1</sub>

5 adenosine receptors on human pulmonary artery endothelial cells. *J Endotoxin Res* 8:  
263-271 (2002); Zamora CA, Baron DA, Heffner JE. Thromboxane contributes to  
pulmonary hypertension in ischemia-reperfusion lung injury. *J Appl Physiol* 74:224-  
229 (1993); Gornikiewicz A, Sautner T, Brostjan C, *et al.* Catecholamines up-  
regulate lipopolysaccharide-induced IL-6 production in human microvascular  
10 endothelial cells. *FASEB J* 14:1093-1100 (2000)). A number of patents propose the  
use of a specific chemical structure A<sub>1</sub> adenosine receptor antagonists and methods of  
use of these A<sub>1</sub> adenosine receptor antagonists as cardiotonics, bronchodilators, and  
biliary anti-spasm agents. *See* U.S. Patent Nos. 4,783,530, 5,032,593, and 3,309,271.

Published U.S. Patent Application 20020058667 proposes A<sub>1</sub> AR antagonist  
15 chemical structures, N-6 substituted 7-deazapurines, and their use for treating a  
disease associated with an A<sub>1</sub> adenosine receptor: cognitive disease, renal failure,  
cardiac arrhythmias, respiratory epithelia, transmitter release, sedation,  
vasoconstriction, bradycardia, negative cardiac inotropy and dromotrophy,  
bronchoconstriction, neutrophil chemotaxis (anti-inflammatory), reflux condition, or  
20 ulcerative condition. This patent application also proposes the use of these specific  
A<sub>1</sub> AR antagonists for therapy for asthma, chronic obstructive pulmonary disease  
(COPD), allergic rhinitis, or upper respiratory disorder alone or in combination with  
other agents.

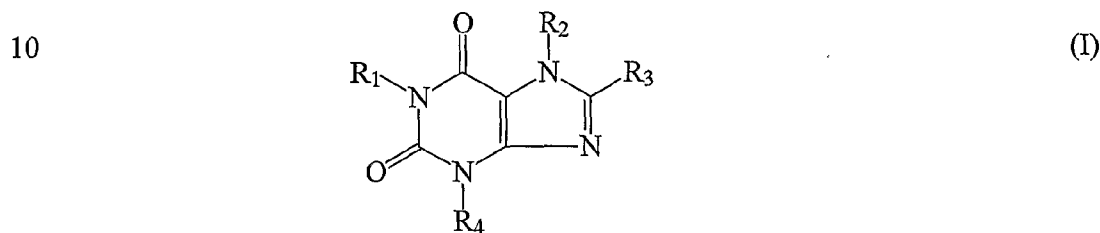
By blocking activation of purinergic receptors, such as A<sub>1</sub> ARs, A<sub>1</sub> AR  
25 antagonists offer a novel, dual mechanism of action for the prevention and early  
treatment of allergic asthma in humans— prevention and treatment of both the  
bronchoconstriction and acute inflammation without the side effects associated with  
many current therapies.

### 30 Summary of the Invention

According to embodiments of the present invention, the present invention  
relates to a method of treating purinoceptor-related disorders, comprising concurrently  
administering an A<sub>1</sub> adenosine receptor antagonist or a P<sub>2X</sub> purinoceptor antagonist  
with at least one additional active agent effective to treat purinoceptor-related  
35 disorders.

5 According to other embodiments of the invention, the present invention relates to a method of treating purinoceptor-related disorders, comprising concurrently administering:

(a) an A<sub>1</sub> adenosine receptor antagonist comprising a compound of Formula I:



15 wherein

R<sub>1</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>8</sub> alkyl;

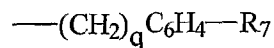
R<sub>2</sub> is of the formula:



wherein n is an integer ranging from 1 to 8; R<sub>5</sub> is H or CH<sub>3</sub>(CH<sub>2</sub>)<sub>p</sub>, wherein p is an integer ranging from 1 to 7; and R<sub>6</sub> is H or (CH<sub>2</sub>)<sub>m</sub>OH, wherein m is an integer

25 ranging from 1 to 8;

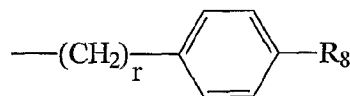
R<sub>3</sub> is of the formula:



30 and

wherein q is an integer ranging from 1 to 8; and wherein R<sub>7</sub> is selected from the group consisting of H, NH<sub>2</sub>, R<sub>9</sub>COOH, wherein R<sub>9</sub> is an alkylene or alkenylene group having 1 to 8 carbon atoms, and (CH<sub>2</sub>)<sub>t</sub>OH, wherein t is an integer ranging from 1 to 8; and

35 R<sub>4</sub> is of the formula:



40 wherein R<sub>8</sub> is selected from the group consisting of H; NH<sub>2</sub>; (CH<sub>2</sub>)<sub>s</sub>OH, wherein s is an integer ranging from 1 to 8; and R<sub>10</sub>COOH, wherein R<sub>10</sub> is an alkylene

- 5 or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8; or a pharmaceutically acceptable salt thereof, or a P<sub>2x</sub> purinoceptor antagonist or pharmaceutically acceptable salt thereof; with
- (b) a compound selected from the group consisting of steroids, *e.g.*, fluticasone, including, but not limited to, fluticasone propionate, beta-2 agonists, *e.g.*,
- 10 salmeterol, xanthines, *e.g.*, theophylline, A<sub>1</sub> adenosine receptor antagonists, A<sub>2a</sub> adenosine receptor agonists, A<sub>2b</sub> adenosine receptor antagonists, A<sub>3</sub> adenosine receptor antagonists, P<sub>2y</sub> purinoceptor agonists, P<sub>2x</sub> purinoceptor antagonists, TNF alpha mAb, TNF alpha antagonists, selectin antagonists, beta-2 integrin blockers, interferon, disease modifying anti-rheumatic drugs (DMARDs), proteasome
- 15 inhibitors, vascular adhesion protein (VAP-1) mAb, neutrophil inhibitory factor (rNIF), immunomodulators, NHE inhibitors, monophosphoryl Lipid A (MPL A), other immune stimulants, including, but not limited to, mycobacterium, endotoxin, interferon-alpha, granulocyte colony stimulating factor (GCSF), granulocyte-macrophage colony stimulating factor (GMCSF), endotoxin antagonists, antifactor IX
- 20 mAb, p38 mitogen-activated protein kinase (p38 MAPK) inhibitor, lipid emulsion, platelet activating factor acetylhydrolase (PAF-AH), CD14 receptor antagonist, caspase inhibitors, protease inhibitors, nitric oxide scavengers, nitric oxide blockers, nitric oxide synthetase inhibitors, re tissue factor protein inhibitors (re TFPI), bactericidal permeabilizing increasing re (BPI) protein fragment, CpG DNA,
- 25 Mycobacterium vaccae, lactobacillus, modified endotoxin – Lipid A, diuretics, vasodilators, anti-platelet agents, anticoagulants, nitrates, calcium channel blockers, beta receptor antagonists, antihypertensives, diuretics, antidepressants, appetite suppressants, mast cell stabilizers, anti-histamines, cetirizine, leukotriene receptor antagonists, anticytokines, phosphodiesterase enzyme inhibitors, 5-lipoxygenase
- 30 inhibitors, platelet activating factor antagonists, thromboxane receptor antagonists, neurokinin receptor antagonists, central nervous system (CNS) stimulants, cognition enhancers, acetylcholinesterase inhibitors, acridine derivative, for example, tetrahydroaminoacridine (tacrine), complement receptor antagonists, cyclosporin, endothelin receptor antagonists, angiotensin enzyme converting (ACE) inhibitors,
- 35 antisense oligonucleotides, anti-IgE, insulin, oral hypoglycemics, smooth muscle relaxants, antibiotics, antiviral agents, antifungal agents, anti-inflammatory agents, also including nonsteroidal anti-inflammatory agents, cancer therapies, narcotics,

5 antitussive agents, surfactants, and combinations thereof, in an amount effective to treat the purinoceptor-related disorder.

According to still other embodiments of the present invention, the present invention relates to a method of treating purinoceptor-related disorders, comprising concurrently administering an A<sub>1</sub> adenosine receptor antagonist or a P<sub>2x</sub> purinoceptor  
10 antagonist with at least one additional active agent effective to treat purinoceptor-related disorders, wherein the purinoceptor-related disorder is selected from the group consisting of, congestive heart failure, hypertension, such as systemic hypertension and pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, renal failure, Alzheimer's disease, depression, obesity, asthma, diabetes,  
15 cystic fibrosis, allergic conditions, including, but not limited to allergic rhinitis and anaphylactic shock, autoimmune disorders, inflammatory disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, postoperative ileus, fibrosis, sclerosis, Adult Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), Severe Acute Respiratory Syndrome (SARS), septicemia,  
20 substance abuse, drug dependence, and Parkinson's disease.

A further embodiment of the present invention is the use of an active agent as described above for the preparation of a medicament for the treatment of a disorder as described above.

According to yet other embodiments of the present invention, the present  
25 invention relates to the use of active compounds as disclosed herein for the manufacture of a medicament for the prophylactic or therapeutic treatment of asthma in a patient in need of such treatment.

### **Detailed Description of Preferred Embodiments**

30 The foregoing and other aspects of the present invention will now be described in more detail with respect to other embodiments described herein. It should be appreciated that the invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully  
35 convey the scope of the invention to those skilled in the art.

The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting

5 of the invention. As used in the description of the invention and the appended claims, the singular forms “a”, “an” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to  
10 which this invention belongs.

All publications, U.S. patent applications, U.S. patents and other references cited herein are incorporated by reference in their entireties.

The term “alkyl” as used herein refers to C1-C20 inclusive, linear, branched, or cyclic, saturated or unsaturated hydrocarbon chains, including for example, methyl,  
15 ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, octyl, ethenyl, propenyl, butenyl, pentyl, hexenyl, octenyl, butadienyl, and allenyl groups. Alkyl groups can either be unsubstituted or substituted with one or more non-interfering substituents, e.g., halogen, alkoxy, acyloxy, hydroxy, mercapto, carboxy, benzyloxy, phenyl, benzyl, or other functionality which has been suitably blocked with a  
20 protecting group so as to render the functionality non-interfering. Each substituent may be optionally substituted with additional non-interfering substituents. The term “non-interfering” characterizes the substituents as not adversely affecting any reactions to be performed in accordance with the process of this invention.

The term “alkenylene” denotes groups formed from straight chain, branched or  
25 cyclic alkenes including ethylenically mono-, di- or poly-unsaturated alkyl or cycloalkyl groups. Non-limiting examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1,4-pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl,  
30 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

The term “A<sub>1</sub> adenosine receptor antagonist” as used herein refers to a compound that partially or completely inhibits the activity of an A<sub>1</sub> adenosine  
35 receptor agonist.

The term “purinoceptor-related disorder” refers to conditions wherein purinoceptor agonists, for example, nucleosides, such as adenosine, adenosine

5 agonists, adenosine triphosphate, or related triphosphate or diphosphate nucleotides, or combinations thereof, play a role in the condition observed.

As used herein, the term “asthma” refers to a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness, airflow limitation which is partially reversible, and respiratory symptoms of wheezing, breathlessness, cough,  
10 and chest tightness. Asthma can be divided into two groups: 1) allergic/extrinsic asthma, and 2) intrinsic/non-atopic asthma associated with asthma attacks provoked by exercise, cold, and psychological stress. Allergic asthma is characterized by an acute, early-stage (immediate) allergic response (EAR) and a late-phase (delayed) allergic response (LAR) characterized by airway inflammation, bronchial  
15 hyperreactivity, and airway damage which can ultimately progress to fibrosis and structural remodeling of airways (Willis-Karp M. Immunologic basis of antigen-induced airway hyperresponsiveness. Annu Rev Immunol 1999; 17:255-281). Rapid mucosal edema, airway narrowing, and mast cell degranulation characterize the early asthmatic response. Binding of IgE produced by antigen presenting B cells triggers  
20 the degranulation of mast cells. The late asthmatic response is characterized by the migration of eosinophils and lymphocytes from the blood into the lung parenchyma and airway epithelium. In both the early and late phase responses, the production of chemotactic factors and cytokines that promote the T lymphocyte type 2 (Th2) immune response, *e.g.* IL-4, IL-5, and IL-13, contributes to the development of  
25 airway reactivity and airflow obstruction.

The term “autoimmune disorder” refers to autoimmune disorders or diseases that can be caused by the failure of the immune system to distinguish self from non-self. In these disorders, the immune system reacts against self tissues and this response can cause inflammation and tissue injury. Autoimmune disorders can be  
30 classified into two basic categories: (1) antibody-mediated diseases including, but not limited to, systemic lupus erythematosus (SLE), pemphigus vulgaris, myasthenia gravis, hemolytic anemia, thrombocytopenia purpura, Grave's disease, Sjogren's disease and dermatomyositis; and (2) cell-mediated diseases including, but not limited to, Hashimoto's disease, polymyositis, inflammatory bowel disease, multiple sclerosis,  
35 diabetes mellitus, ulcerative colitis, rheumatoid arthritis, and scleroderma. As used herein, an autoimmune disorder may be or have the clinical manifestations of an inflammatory disorder.

5           The term “bronchodilating agent” as used herein refers to an agent that prevents, reduces, or reverses the degree of airway constriction. Examples of bronchodilating agents include, but are not limited to,  $\beta$ -2 adrenergic agonists, methylxanthines, including, but not limited to theophylline, theobromine, and caffeine, anti-cholinergics, anti-histamines, leukotriene receptor antagonists, and  
10 phosphodiesterase inhibitors.

          As used herein, the term “anti-inflammatory agent” refers to an agent that prevents or inhibits the signs and symptoms of inflammation. Examples of anti-inflammatory agents include, but are not limited to, glucocorticoids, cromolyn, and nonsteroidal anti-inflammatory drugs. However, it is noted that a “bronchodilating  
15 agent” may have anti-inflammatory properties and an “anti-inflammatory agent” may have bronchodilating properties.

          The term “treat” as used herein refers to any type of treatment that imparts a benefit to a patient afflicted with a disease, including improvement in the condition of the patient (*e.g.*, in one or more symptoms), delay in the progression of the disease,  
20 etc.

          As used herein, a treatment effective amount is an amount effective to result in improvement in the condition of the patient (*e.g.*, in one or more symptoms), delay in the progression of the disease, etc.

          The term “pharmaceutically acceptable” as used herein means that the  
25 compound or composition is suitable for administration to a subject to achieve the treatments described herein, without unduly deleterious side effects in light of the severity of the disease and necessity of the treatment.

          As used herein, the word “concurrently” means sufficiently close in time to produce a combined effect (that is, concurrently may be simultaneously, or it may be two  
30 or more events occurring within a short time period before or after each other).

          As used herein, the administration of two or more compounds “in combination” means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds may be administered simultaneously (*i.e.*, concurrently) or sequentially. Additionally,  
35 simultaneous administration may be carried out by mixing the compounds prior to administration, or by administering the compounds at the same point in time but at different anatomic sites or using different routes of administration.

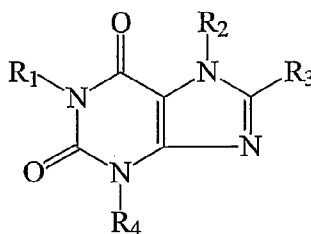
5           The phrases "concurrent administration," "administration in combination,"  
"simultaneous administration" or "administered simultaneously" as used herein,  
interchangeably mean that the compounds are administered at the same point in time  
or immediately following one another. In the latter case, the two compounds are  
administered at times sufficiently close that the results observed are indistinguishable  
10 from those achieved when the compounds are administered at the same point in time.

Suitable subjects to be treated according to the present invention include both  
avian and mammalian subjects, preferably mammalian. Mammals according to the  
present invention include but are not limited to canine, felines, bovines, caprines,  
equines, ovines, porcines, rodents (*e.g.* rats and mice), lagomorphs, primates, and the  
15 like, and encompass mammals *in utero*. Humans are preferred. Human subjects of  
both genders and at any stage of development (*i.e.*, neonate, infant, juvenile,  
adolescent, adult) can be treated according to the present invention.

Illustrative avians according to the present invention include chickens, ducks,  
turkeys, geese, quail, pheasant, ratites (*e.g.*, ostrich) and domesticated birds (*e.g.*,  
20 parrots and canaries), and include birds *in ovo*. Chickens and turkeys are preferred.  
Any mammalian subject in need of being treated according to the present invention is  
suitable. The present invention is primarily concerned with the treatment of human  
subjects, but the invention may also be carried out on animal subjects, particularly  
mammalian subjects such as mice, rats, dogs, cats, livestock and horses for veterinary  
25 purposes, and for drug screening and drug development purposes.

### 1. Active compounds.

The methods of the present invention include the administration of compounds  
of Formula I, while pharmaceutical compositions of the present invention comprise  
30 compounds of Formula I. As used herein, a compound of Formula I is as follows:



5 wherein

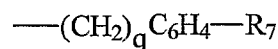
$R_1$  is selected from the group consisting of  $C_1$ - $C_8$  alkyl;

$R_2$  is of the formula:



wherein  $n$  is an integer ranging from 1 to 8;  $R_5$  is H or  $CH_3(CH_2)_p$ , wherein  $p$  is an integer ranging from 1 to 7; and  $R_6$  is H or  $(CH_2)_mOH$ , wherein  $m$  is an integer ranging from 1 to 8;

15  $R_3$  is of the formula:



and

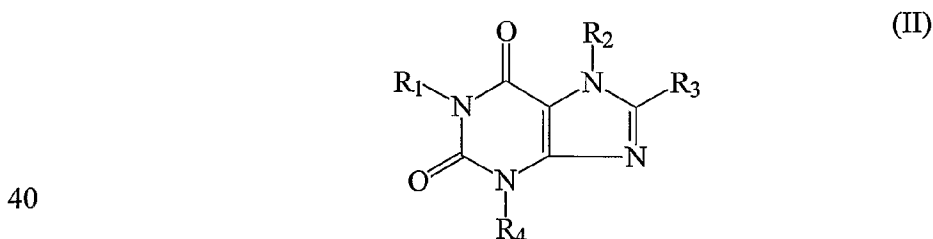
20 wherein  $q$  is an integer ranging from 1 to 8; and wherein  $R_7$  is selected from the group consisting of H,  $NH_2$ ,  $R_9COOH$ , wherein  $R_9$  is an alkylene or alkenylene group having 1 to 8 carbon atoms, and  $(CH_2)_tOH$ , wherein  $t$  is an integer ranging from 1 to 8; and

$R_4$  is of the formula:

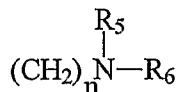


wherein  $R_8$  is selected from the group consisting of H;  $NH_2$ ;  $(CH_2)_sOH$ , wherein  $s$  is an integer ranging from 1 to 8; and  $R_{10}COOH$ , wherein  $R_{10}$  is an alkylene or alkenylene group having 1 to 8 carbon atoms; and  $r$  is an integer ranging from 1 to 8; or a pharmaceutically acceptable salt thereof.

The methods of the present invention also include the administration of a compound of Formula II, while pharmaceutical compositions of the present invention comprises a compound of Formula II. As used herein, a compound of Formula I is as follows:

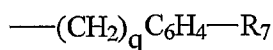


- 5 wherein R<sub>1</sub> is C<sub>3</sub> alkyl;  
R<sub>2</sub> is of the formula:



10

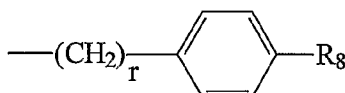
wherein n is 2; R<sub>5</sub> is CH<sub>3</sub>(CH<sub>2</sub>)<sub>p</sub>, wherein p is 1; R<sub>6</sub> is (CH<sub>2</sub>)<sub>m</sub>OH, wherein m is 2;  
R<sub>3</sub> is of the formula:



15

and

wherein q is 1; R<sub>7</sub> is H; and  
R<sub>4</sub> is of the formula:



20

wherein R<sub>8</sub> is NH<sub>2</sub>; and r is 2; or a pharmaceutically acceptable salt thereof.

The synthesis of the compound according to the Formula I is described in detail  
in U.S. Patent No.5,786,360 and 6,489,332 to Neely.

- 25 The methods of the present invention also include the administration of A<sub>1</sub>  
receptor antagonists and P<sub>2X</sub> receptor antagonists. Examples of A<sub>1</sub> receptor antagonists  
include, but are not limited to, alkyl xanthines such as 8-cyclopentyl-1,3-  
dipropylxanthine (DPCPX), xanthine amine cogener (XAC), xanthine carboxylic  
cogener (XCC), 1,3-dipropyl-8-(3-noradamantyl) xanthine (KW 3902), 1,3-dipropyl-  
30 8-(dicyclopropylmethyl)xanthine (KF 15372), 1,3-dipropyl-S-(3-oxocyclopentyl  
xanthine (KFM 19), 1-propyl-3-(4-amino-3-iodophenethyl)-8-cyclopentylxanthine  
(BW-A844U), 1,3-dipropyl-8-sulfophenylxanthine (DPSPX), cyclopentyl  
theophylline (CPT) and 7-[2-ethyl (2-hydroxyethyl) amino]-ethyl]-3,7-dihydro-1,3 -  
dimethyl-8-(phenylmethyl)-1H-purine-2,6-dione (Bamifylline (BAM)), 8-  
35 cyclopentyl-3-(3-((4-fluorosulfonylbenzoyl)-oxy)propyl)-1-propylxanthine  
(FSCPX), 1,3-dipropyl-8-(3-noradamantyl)xanthine (NAX); 1,3-dipropyl-8-[2(5,6-  
epoxy)norbornyl]xanthine (ENX), 8-(1(R)-Methyl-2-phenylethyl)-1,3-dipropyl-7H-  
xanthine (MDL 102503); N<sup>6</sup>, 9-methyl adenines such as (±) N<sup>6</sup> -endonorbornan-2-yl-  
9-methyladenine (N-0861); N<sup>6</sup>, 9-disubstituted adenines; 2-phenyl-7-deazaadenines

- 5 such as (R)-7,8-dimethyl-2-phenyl-9-(1-phenylethyl)-7-deazaadenine; 3-(2-substituted-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5- $\alpha$ ]pyridines, such as 7,8-dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1H-imidazo[2,1-i]purin-5(4H)-one; ( $\pm$ )-R-1-[( $\epsilon$ )-3[2-]phenylpyrazolo(1,5- $\alpha$ )pyridin-3-yl]acryloyl]-2-piperidine ethanol; 8-azaxanthines such as 7-cyclopentyl-1,3-dipropyl-8-azaxanthine;
- 10 pyrazolo[3,4-*c*]quinolines; pyrazolo-[1,5- $\alpha$ ]pyridines, such as (E)-R-1-(1-Oxo-3-(2-phenylpyrazolo(1,5- $\alpha$ )pyridin-3-yl)-2-propenyl)-2-piperidineacetic acid (FK 352), 3-(2-(3-Carboxypropyl)-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo(1,5- $\alpha$ )pyridine (FK 838), 2-Piperidineethanol, 1-(1-oxo-3-(2-phenylpyrazolo(1,5 $\alpha$ )pyridin-3-yl)-2-propenyl)-, (R-(E)) (FK 453) ; 1,8-naphthyridines; (3-phenyl)-1,2,4-thiadiazoles such as *N*-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-methoxybenzamide (LUF 5417); 4-phenyl-2-(phenylcarboxamido)-1,3-thiazole, *N*-(4-Phenylthiazol-2-yl)-4-methoxybenzamide (LUF 5433); 3-Aryl[1,2,4]triazolo[4,3- $\alpha$ ]benzimidazol-4(10H)ones (ATBIs); Imidazol[1,2- $\alpha$ ]quinoxalin-4-amines, such as *N*-cyclopentylamino-1-methylimidazo(1,2- $\alpha$ )quinoxalin-4-amine (IRFI 165);
- 20 triazoloquinazolines; 1,2,4-Triazolo[4,3- $\alpha$ ]quinoxalin-1-ones; and 2-arylpyrazolo[3,4-*c*]quinolines.

- Examples of P<sub>2X</sub> receptor antagonists include, but are not limited to, pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS), pyridoxal-5'-phosphate-6-azophenyl]-2',5'-disulfonate (iso-PPADS);  $\alpha,\beta$ -Me ATP; 4,4'-
- 25 diisothiocyanatostilbene-2,2'-disulphonate (DIDS); isoquinoline sulfonamide 1-[*N,O*-bis(5-isoquinoline-sulfonyl)-*N*-methyl-L-tyrosyl]-4-phenylpiperazine (KN-62); trinitrophenyl (TNP)-substituted nucleotides (TNP-ATP); diinosine pentaphosphate (IP<sub>5</sub>I); PPADS analogs, pyridoxine cyclic phosphate, such as cyclic pyridoxine- $\alpha$ -monophosphate-6-phenylazo-2',5'-disulfonate (MRS 2220) and pyridoxal-5'-
- 30 phosphate-6-(2'-naphthylazo-6'-nitro-4',8'-disulfonate (PPNDS); suramin; suramin analogues, such as 8-(benzamido)naphthalene-1,3,5-trisulfonate (NF023); 8,8'-(carbonylbis(imino-4,1-phenylenecarbonylimino-4,1-phenylenecarbonylimino))bis(1,3,5-naphthalenetrisulfonic acid (NF279); and 4,4',4'',4''-(carbonylbis(imino-5,1,3-benzenetriyl-bis(carbonylimino)))tetrakis-
- 35 benzene-1,3-disulfonic acid (NF449).

For the sake of simplicity, Formulas I and II herein illustrate the active compounds in the naturally occurring D configuration, but the present invention also

5 encompasses compounds in the L configuration, and mixtures of compounds in the D and L configurations, unless otherwise specified. The naturally occurring D configuration is preferred.

The active compounds disclosed herein can, as noted above, be prepared in the form of their pharmaceutically acceptable salts. Pharmaceutically acceptable salts are  
10 salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic  
15 acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; (b) salts formed from elemental anions such as chlorine, bromine, and iodine, and (c) salts derived from bases, such as ammonium  
20 salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, and salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine.

## 2. Methods of Use

25 The present invention provides a method of treating purinoceptor receptor-related disorders, comprising concurrently administering an A<sub>1</sub> adenosine receptor antagonist or a P<sub>2X</sub> purinoceptor antagonist with at least one additional active agent effective to treat purinoceptor-related disorders. Purinergic compounds which may interact with adenosine receptors include the naturally present adenosine and ATP or  
30 the synthetic adenosine analogues, and are well known to exert multiple functions in almost every tissue of the body, but are particularly conspicuous and therefore have been extensively studied in the brain where general antinociceptive (analgesic or even anesthetic), antiepileptic and tissue protective effects are well documented. *See* U.S. Patent No. 6,015,835 to Miyamoto. Purinoceptors have been associated with  
35 disorders and conditions cited above and those including, but not limited to, congestive heart failure, hypertension, such as systemic hypertension and pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, renal

5 failure, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, allergic conditions, including, but not limited to allergic rhinitis and anaphylactic shock, autoimmune disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, postoperative ileus, fibrosis, sclerosis, septicemia, Adult Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI),  
10 Severe Acute Respiratory Syndrome (SARS), substance abuse, drug dependence, and Parkinson's disease. It has also been shown that administration of compositions comprising selective A<sub>1</sub> adenosine receptor antagonists and/or P<sub>2X</sub> receptor antagonists can prevent injuries related to ischemia followed by reperfusion in an organ, and A<sub>1</sub> adenosine receptor antagonists and/or P<sub>2X</sub> receptor antagonists have  
15 been implicated in the prevention and treatment of ischemia-reperfusion and endotoxin-related tissue injuries. See U.S. Patent Nos. 6,001,842; 5,733,916; and 5,504,090 to Neely. Administration of compositions comprising selective A<sub>1</sub> adenosine receptor antagonists and/or P<sub>2X</sub> receptor antagonists have also been implicated in the prevention and treatment of fibrosis and sclerosis. See U.S. Patent  
20 No. 6,117,445 to Neely.

Thus, the A<sub>1</sub> adenosine receptor antagonists or P<sub>2X</sub> receptor antagonists compounds, compositions, and formulations of the present invention concurrently administered with at least one additional active agent effective to treat purinoceptor-related disorders as provided in the present invention, provide useful therapeutic  
25 methods of preventing and treating purinoceptor-related disorders. Such purinoceptor-related disorders include, but are not limited to, congestive heart failure, hypertension, for example, systemic hypertension and pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, renal failure, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, chronic  
30 obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, postoperative ileus, fibrosis, sclerosis, autoimmune disorders, allergic conditions, including, but not limited to allergic rhinitis and anaphylactic shock, inflammatory disorders, Adult Respiratory Distress Syndrome (ARDS), including Severe Acute Respiratory Syndrome (SARS) and Acute Lung Injury (ALI), septicemia, substance  
35 abuse, drug dependence, and Parkinson's disease.

Agents known to be effective to treat purinoceptor-related disorders can be administered in combination with the compounds and compositions of the present

5 invention with the proviso that combination therapies currently known to specifically  
treat known purinoceptor-related disorders are not contemplated by the present  
invention. Examples of such agents include, but are not limited to, steroids, *e.g.*,  
fluticasone, including but not limited to, fluticasone propionate, beta agonists such as  
beta 2 agonists, *e.g.*, salmeterol, xanthines, *e.g.*, theophylline, A<sub>1</sub> adenosine receptor  
10 antagonists, A<sub>2a</sub> adenosine receptor agonists, A<sub>2b</sub> adenosine receptor antagonists, A<sub>3</sub>  
adenosine receptor antagonists, P<sub>2y</sub> purinoceptor agonists, P<sub>2x</sub> purinoceptor  
antagonists, TNF mAb, TNF antagonists, selectin antagonists, beta-2 integrin  
blockers, interferon, disease modifying anti-rheumatic drugs (DMARDs), proteasome  
inhibitors, VAP-1 mAb, rNIF, immunomodulators, NHE inhibitors, monophosphoryl  
15 Lipid A (MPL A), other immune stimulants, including, but not limited to,  
mycobacterium, endotoxin, interferon-alpha, granulocyte colony stimulating factor  
(GCSF), granulocyte-macrophage colony stimulating factor (GMCSF), endotoxin  
antagonists, antifactor IX mAb, p38 MAPK inhibitor, lipid emulsion, PAF  
acetylhydrolase, CD14 receptor antagonist, caspase inhibitors, protease inhibitors,  
20 nitric oxide scavengers, nitric oxide blockers, nitric oxide synthetase inhibitors, re  
tissue factor protein inhibitors (re TFPI), bactericidal permeabilizing increasing re  
(BPI) protein fragment, CpG DNA, Mycobacterium vaccae, lactobacillus, modified  
endotoxin – Lipid A, diuretics, vasodilators, anti-platelet agents, anticoagulants,  
nitrates, calcium channel blockers, beta receptor antagonists, antihypertensives,  
25 diuretics, antidepressants, appetite suppressants, mast cell stabilizers, anti-histamines,  
cetirizine, leukotriene receptor antagonists, anticytokines, phosphodiesterase enzyme  
inhibitors, 5-lipoxygenase inhibitors, platelet activating factor antagonists,  
thromboxane receptor antagonists, neurokinin receptor antagonists, central nervous  
system (CNS) stimulants, cognition enhancers, acetylcholinesterase inhibitors,  
30 acridine derivative, for example, tetrahydroaminoacridine (tacrine), complement  
receptor antagonists, cyclosporin, endothelin receptor antagonists, angiotensin  
enzyme converting (ACE) inhibitors, antisense oligonucleotides, anti-IgE, insulin,  
hypoglycemics, smooth muscle relaxants, antibiotics, antiviral agents, antifungal  
agents, anti-inflammatory agents, also including nonsteroidal anti-inflammatory  
35 agents, cancer therapies, narcotics, antitussive agents, and surfactants. The  
compounds and compositions of the present invention can be administered with one

- 5 or more of the agents described above which include analogs thereof and isolated and recombinant forms of the agents.

### 3. Pharmaceutical formulations.

The active compounds described above may be formulated for administration  
10 in a pharmaceutical carrier in accordance with known techniques. *See, e.g.*,  
Remington, *The Science And Practice of Pharmacy* (9<sup>th</sup> Ed. 1995). In the  
manufacture of a pharmaceutical formulation according to the invention, the active  
compound (including the physiologically acceptable salts thereof) is typically  
admixed with, *inter alia*, an acceptable carrier. The carrier must, of course, be  
15 acceptable in the sense of being compatible with any other ingredients in the  
formulation and must not be deleterious to the patient. The carrier may be a solid or a  
liquid, or both, and is preferably formulated with the compound as a unit-dose  
formulation, for example, a tablet, which may contain from 0.01 or 0.5% to 95% or  
99% by weight of the active compound. One or more active compounds may be  
20 incorporated in the formulations of the invention, which may be prepared by any of  
the well-known techniques of pharmacy consisting essentially of admixing the  
components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal,  
topical, buccal (e.g., sub-lingual), vaginal, parenteral (e.g., subcutaneous,  
25 intramuscular, intradermal, or intravenous), topical (*i.e.*, both skin and mucosal  
surfaces, including airway surfaces), intraarticular, transdermal, nasal, and  
inhalational administration, although the most suitable route in any given case will  
depend on the nature and severity of the condition being treated and on the nature of  
the particular active compounds which is being used.

30 Formulations suitable for oral administration may be presented in discrete  
units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined  
amount of the active compound; as a powder or granules; as a solution or a  
suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil  
emulsion. Such formulations may be prepared by any suitable method of pharmacy  
35 which includes the step of bringing into association the active compound and a  
suitable carrier (which may contain one or more accessory ingredients as noted  
above). In general, the formulations of the invention are prepared by uniformly and

5 intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a  
10 free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sub-lingual) administration include lozenges  
15 comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration comprise sterile aqueous and non-aqueous injection solutions of the active compound,  
20 which preparations are preferably isotonic with the blood of the intended recipient. These preparations may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions may include suspending agents and thickening agents. The formulations may be presented in unit/dose or multi-dose containers, for  
25 example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or water-for-injection immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. For example, in one aspect of the present invention, there  
30 is provided an injectable, stable, sterile composition comprising a compound of Formula I or II, A<sub>1</sub> adenosine receptor antagonists or P<sub>2X</sub> purinoceptor antagonists, or a salt thereof, in a unit dosage form in a sealed container. The compound or salt is provided in the form of a lyophilizate which is capable of being reconstituted with a suitable pharmaceutically acceptable carrier to form a liquid composition suitable for  
35 injection thereof into a subject. The unit dosage form typically comprises from about 10 mg to about 10 grams of the compound or salt. When the compound or salt is substantially water-insoluble, a sufficient amount of emulsifying agent which is

5     physiologically acceptable may be employed in sufficient quantity to emulsify the compound or salt in an aqueous carrier. One such useful emulsifying agent is phosphatidyl choline.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with  
10     one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include petroleum jelly, lanoline, polyethylene glycols, alcohols,  
15     transdermal enhancers, and combinations of two or more thereof.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration may also be delivered by iontophoresis (*see*, for example,  
20     *Pharmaceutical Research* **3** (6):318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis/tris buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2M active ingredient.

Further, the present invention provides liposomal formulations of the  
25     compounds disclosed herein and salts thereof. The technology for forming liposomal suspensions is well known in the art. When the compound or salt thereof is an aqueous-soluble salt, using conventional liposome technology, the same may be incorporated into lipid vesicles. In such an instance, due to the water solubility of the compound or salt, the compound or salt will be substantially entrained within the  
30     hydrophilic center or core of the liposomes. The lipid layer employed may be of any conventional composition and may either contain cholesterol or may be cholesterol-free. When the compound or salt of interest is water-insoluble, again employing conventional liposome formation technology, the salt may be substantially entrained within the hydrophobic lipid bilayer which forms the structure of the liposome. In  
35     either instance, the liposomes which are produced may be reduced in size, as through the use of standard sonication and homogenization techniques.

5           Of course, the liposomal formulations containing the compounds disclosed herein or salts thereof, may be lyophilized to produce a lyophilizate which may be reconstituted with a pharmaceutically acceptable carrier, such as water, to regenerate a liposomal suspension.

          The compounds and compositions of the present invention can be  
10 administered by any means that transports the active agents to the lung, including but not limited to nasal administration, inhalation, and insufflation. The active agents disclosed herein can be administered to the lungs of a patient by any suitable means, but are preferably administered by generating an aerosol comprised of respirable particles, the respirable particles comprised of the active agents, which particles the  
15 subject inhales. The respirable particles can be liquid or solid, and they can optionally contain other therapeutic ingredients, including, but not limited to surfactants.

          Particles comprised of active agents for practicing the present invention should be administered as a formulation including particles of respirable size: that is, particles of a size sufficiently small to pass through the nose, mouth and larynx upon  
20 inhalation and into the bronchi and alveoli of the lungs. In general, respirable particles range from about 0.5 to 10 microns in diameter. Particles of non-respirable size that are included in the aerosol tend to deposit in the throat and be swallowed. Accordingly, the quantity of non-respirable particles in the aerosol is preferably minimized. For nasal administration, a particle size in the range of 10-500  $\mu\text{m}$  is  
25 preferred to ensure retention in the nasal cavity. Alternatively, droplets can be given.

          Liquid pharmaceutical compositions of active agents for producing an aerosol can be prepared by combining the active agents with a suitable vehicle, such as sterile pyrogen free water. Other therapeutic compounds can optionally be included.

          Solid particulate compositions containing respirable dry particles of  
30 micronized active agents can be prepared by grinding dry antisense compound with a mortar and pestle, and then passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprising the active agent can optionally contain a dispersant that serves to facilitate the formation of an aerosol. A suitable dispersant is lactose, which can be blended  
35 with the active agents in any suitable ratio e.g., a 1 to 1 ratio by weight. The aerosols of liquid particles comprising the active agents can be produced by any suitable means, such as with a nebulizer. See e.g., U.S. Pat. No. 4,501,729.

5           Nebulizers are commercially available devices which transform solutions or  
suspensions of the active ingredient into a therapeutic aerosol mist either by means of  
acceleration of a compressed gas, typically air or oxygen, through a narrow venturi  
orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers  
consist of the active ingredient in a liquid carrier, the active ingredient comprising up  
10 to 40% w/w, but preferably less than 20% w/w, of the formulation. The carrier is  
typically water or a dilute aqueous alcoholic solution, preferably made isotonic with  
body fluids by the addition of, for example, sodium chloride. Optional additives  
include preservatives if the formulation is not prepared sterile, for example, methyl  
hydroxybenzoate, antioxidants, flavoring agents, volatile oils, buffering agents and  
15 surfactants.

The aerosols of solid particles comprising the active agents can likewise be  
produced with any solid particulate medicament aerosol generator. Aerosol generators  
for administering solid particulate medicaments to a subject produce particles, which  
are respirable, as explained above, and generate a volume of aerosol containing a  
20 predetermined metered dose of a medicament at a rate suitable for human  
administration. One illustrative type of solid particulate aerosol generator is an  
insufflator. Suitable formulations for administration by insufflation include finely  
comminuted powders that can be delivered by means of an insufflator or taken into  
the nasal cavity in the manner of a snuff. In the insufflator, the powder, e.g., a  
25 metered dose thereof effective to carry out the treatments described herein, is  
contained in capsules or cartridges, typically made of gelatin or plastic, which are  
either pierced or opened in situ and the powder delivered by air drawn through the  
device upon inhalation or by means of a manually-operated pump. The powder  
employed in the insufflator consists either solely of the active ingredient or of a  
30 powder blend comprising the active ingredient, a suitable powder diluent, such as  
lactose, and an optional surfactant. The active ingredient typically comprises from 0.1  
to 100 w/w of the formulation. A second type of illustrative aerosol generator  
comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol  
dispensers, typically containing a suspension or solution formulation of the active  
35 ingredient in a liquefied propellant. During use these devices discharge the  
formulation through a valve adapted to deliver a metered volume, typically from 10 to  
150  $\mu$ l, to produce a fine particle spray containing the active ingredient. Suitable

- 5     propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation can additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents.
- 10             The aerosol, whether formed from solid or liquid particles, can be produced by the aerosol generator at a rate of from about 10 to 150 liters per minute, more preferably from about 30 to 150 liters per minute, and most preferably about 60 liters per minute. Aerosols containing greater amounts of medicament can be administered more rapidly.
- 15             Any propellant may be used in carrying out the present invention, including both chlorofluorocarbon-containing propellants and non-chlorofluorocarbon-containing propellants. Thus, fluorocarbon aerosol propellants that may be employed in carrying out the present invention including fluorocarbon propellants in which all hydrogens are replaced with fluorine, chlorofluorocarbon propellants in which all hydrogens are
- 20     replaced with chlorine and at least one fluorine, hydrogen-containing fluorocarbon propellants, and hydrogen-containing chlorofluorocarbon propellants. Examples of such propellants include, but are not limited to:  $\text{CF}_3\text{-CHF-CF}_2\text{H}$ ;  $\text{CF}_3\text{-CH}_2\text{-CF}_2\text{H}$ ;  $\text{CF}_3\text{-CHF-CF}_3$ ;  $\text{CF}_3\text{-CH}_2\text{-CF}_3$ ;  $\text{CF}_3\text{-CHCl-CF}_2\text{Cl}$ ;  $\text{CF}_3\text{-CHCl-CF}_3$ ;  $\text{cy-C}(\text{CF}_2)_3\text{-CHCl}$ ;  $\text{CF}_3\text{-CHCl-CH}_2\text{Cl}$ ;  $\text{CF}_3\text{-CHF-CF}_2\text{Cl}$ ;  $\text{CF}_3\text{-CHCl-CFHCl}$ ;  $\text{CF}_3\text{-CFCl-CFHCl}$ ;  $\text{CF}_3\text{-CF}_2\text{-CF}_2\text{H}$ ;  $\text{CF}_3\text{-CF}_2\text{-CH}_3$ ;  $\text{CF}_2\text{H-CF}_2\text{-CFH}_2$ ;  $\text{CF}_3\text{-CF}_2\text{-CFH}_2$ ;  $\text{CF}_3\text{-CF}_2\text{-CH}_2\text{Cl}$ ;  $\text{CF}_2\text{H-CF}_2\text{-CH}_3$ ;  $\text{CF}_2\text{H-CF}_2\text{-CH}_2\text{Cl}$ ;  $\text{CF}_3\text{-CF}_2\text{-CF}_2\text{-CH}_3$ ;  $\text{CF}_3\text{-CF}_2\text{-CF}_2\text{-CF}_2\text{H}$ ;  $\text{CF}_3\text{-CHF-CHF-CF}_3$ ;  $\text{CF}_3\text{-O-CF}_3$ ;  $\text{CF}_3\text{-O-CF}_2\text{H}$ ;  $\text{CF}_2\text{H-H-O-CF}_2\text{H}$ ;  $\text{CF}_2\text{H-O-CFH}_2$ ;  $\text{CF}_3\text{-O-CH}_3$ ;  $\text{CF}_3\text{-O-CF}_2\text{-CF}_2\text{H}$ ;  $\text{CF}_3\text{-O-CF}_2\text{-O-CF}_3$ ;  $\text{cy-CF}_2\text{-CF}_2\text{-O-CF}_2\text{-}$ ;  $\text{cy-CHF-CF}_2\text{-O-CF}_2\text{-}$ ;  $\text{cy-CH}_2\text{-CF}_2\text{-O-CF}_2\text{-}$ ;  $\text{cy-CF}_2\text{-O-CF}_2\text{-O-CF}_2\text{-}$ ;  $\text{CF}_3\text{-O-CF}_2\text{-Br}$ ;  $\text{CF}_2\text{H-O-CF}_2\text{-Br}$ ; and mixtures thereof, where "cy" denotes a cyclic compound in which the end terminal covalent bonds of the structures shown are the same so that the end terminal groups are covalently bonded together. Particularly preferred are hydrofluoroalkanes such as 1,1,1,2-tetrafluoroethane (propellant 134a) and heptafluoropropane (propellant 227). A stabilizer such as a fluoropolymer may optionally be included in formulations of fluorocarbon propellants,
- 35     such as described in U.S. Patent No. 5,376,359 to Johnson, the disclosure of which is incorporated herein by reference in its entirety.

5           Other pharmaceutical compositions may be prepared from the water-insoluble compounds disclosed herein, or salts thereof, such as aqueous base emulsions. In such an instance, the composition will contain a sufficient amount of pharmaceutically acceptable emulsifying agent to emulsify the desired amount of the compound or salt thereof. Particularly useful emulsifying agents include phosphatidyl  
10   cholines, and lecithin.

          In addition to compounds of Formula I and II, A<sub>1</sub> adenosine receptor antagonists or P<sub>2x</sub> purinoceptor antagonists, or their salts, the pharmaceutical compositions may contain other additives, such as pH-adjusting additives. In particular, useful pH-adjusting agents include acids, such as hydrochloric acid, bases  
15   or buffers, such as sodium lactate, sodium acetate, sodium phosphate, sodium citrate, sodium borate, or sodium gluconate. Further, the compositions may contain microbial preservatives. Useful microbial preservatives include methylparaben, propylparaben, and benzyl alcohol. The microbial preservative is typically employed when the formulation is placed in a vial designed for multidose use. Of course, as indicated, the  
20   pharmaceutical compositions of the present invention may be lyophilized using techniques well known in the art.

#### 4.       **Dosage and routes of administration.**

          As noted above, the present invention provides pharmaceutical formulations  
25   comprising the active compounds (including the pharmaceutically acceptable salts thereof), in pharmaceutically acceptable carriers for oral, rectal, topical, buccal, parenteral, intramuscular, intradermal, or intravenous, transdermal, intraarticular, nasal, and inhalational administration.

          According to the present invention, methods of this invention comprise  
30   administering an effective amount of a composition of the present invention as described above to the subject. The effective amount of the composition, the use of which is in the scope of present invention, will vary somewhat from subject to subject, and will depend upon factors such as the age and condition of the subject and the route of delivery. Such dosages can be determined in accordance with routine  
35   pharmacological procedures known to those skilled in the art. For example, the compounds of the present invention can be administered to the subject in an amount ranging from a lower limit from about 0.01, 0.05, 0.10, 0.50, 1.0, 5.0, or 10% to an

- 5 upper limit ranging from about 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, 96, 97, 98, 99, or  
100% by weight of the composition. In some embodiments, the compounds comprise  
from about 0.05 to about 95% by weight of the composition. In other embodiments,  
the compounds comprise from about 0.05 to about 60% by weight of the composition.  
In still other embodiments, the compounds comprise from about 0.05 to about 10% by  
10 weight of the composition.

- The therapeutically effective dosage of any specific compound will vary  
somewhat from compound to compound, patient to patient, and will depend upon the  
condition of the patient and the route of delivery. As a general proposition, a dosage  
from about 0.1 to about 50 mg/kg will have therapeutic efficacy, with still higher  
15 dosages potentially being employed for oral administration, wherein aerosol  
administration is usually lower than oral or intravenous administration. Toxicity  
concerns at the higher level may restrict intravenous dosages to a lower level such as  
up to about 10 mg/kg, all weights being calculated based upon the weight of the active  
base, including the cases where a salt is employed. Typically a dosage from about 0.5  
20 mg/kg to about 5 mg/kg will be employed for intravenous or intramuscular  
administration. A dosage from about 10 mg/kg to about 50 mg/kg may be employed  
for oral administration.

- In particular embodiments, administration to a subject such as a human, a  
dosage of from about 0.01, 0.1, or 1 mg/kg up to 50, 100, or 150 mg/kg or more for  
25 each active agent can be employed. Depending on the solubility of the particular  
formulation of active compounds administered, the daily dose can be divided among  
one or several unit dose administrations. The administration of the active compounds  
can be carried out therapeutically (i.e., as a rescue treatment) or prophylactically.

- The present invention is explained in greater detail in the following non-  
30 limiting Examples.

5

**EXAMPLE 1**

*In vitro* pharmacology studies performed support the finding that the A<sub>1</sub> receptor antagonists of the present invention have a high affinity for the human A<sub>1</sub> AR (0.58 μM). The protein source for the human A<sub>1</sub> ARs in these pharmacological studies was obtained from membranes from human pulmonary artery endothelial cells purchased from BioWhittaker Inc. (Walkersville, MD). This protein source for the human A<sub>1</sub> AR was not obtained from a cell line transfected with a recombinant human A<sub>1</sub> AR. As shown below in Table 1, the pharmacology studies demonstrate that the affinity of the compounds as antagonists for the human A<sub>1</sub> AR (L-97-1) is approximately 3 – 10 times that of bamiphylline which binds to human A<sub>2a</sub> AR.

**TABLE 1** Affinities of L-97-1 and other adenosine receptor ligands for Human A<sub>1</sub> adenosine receptor

Ligand	Human A <sub>1</sub> ( <sup>125</sup> I-BWA844U)				Human A <sub>1</sub> ( <sup>3</sup> H-DPCPX)		
	IC <sub>50</sub> (μM)	K <sub>i</sub> (μM)	IC <sub>50</sub> (μg/ml)	N	IC <sub>50</sub> (μM)	K <sub>i</sub> (μM)	IC <sub>50</sub> (μg/ml)
L-97-1	2.077 ± 0.712	1.13 ± 0.39	1.077 ± 0.369	3	1.421 ± 0.567	0.580 ± 0.330	0.737 ± 0.294
Bamiphylline	20.150 ± 12.65	11.05 ± 6.95	8.483 ± 5.325	2	3.770 ± 0.964	1.927 ± 0.517	1.587 ± 0.406
DPCPX	13.2 ± 1.2	7.19 ± 0.654	4.013 ± 0.365	3	0.076 ± 0.036	0.038 ± 0.018	0.023 ± 0.011
CCPA					0.034 ± 0.023	0.017 ± 0.012	0.013 ± 0.009

Bamiphylline binds to the human A<sub>2a</sub> AR (27 μM). L-97-1 does not bind to the human A<sub>2a</sub> AR (>100 μM). Neither L-97-1 (> 100 μM) nor bamiphylline (> 100 μM) bind to the human A<sub>2b</sub> AR.

20

5

**EXAMPLE 2**

*In vitro* pharmacology studies performed support the finding that the A<sub>1</sub> receptor antagonists of the present invention are highly selective for the human A<sub>1</sub> adenosine receptor versus human A<sub>2a</sub> and A<sub>2b</sub> ARs and the rat A<sub>3</sub> AR as shown in the table below.

10

**TABLE 2** Affinities of L-97-1 and other adenosine receptor ligands for Human A<sub>2a</sub>, A<sub>2b</sub>, and Rat A<sub>3</sub> adenosine receptor subtypes

Ligand	Human A <sub>2a</sub> ( <sup>3</sup> H-CGS21680)			Human A <sub>2b</sub> ( <sup>3</sup> H-DPCPX)			Rat A <sub>3</sub> ( <sup>125</sup> I-AB-MECA)		
	IC <sub>50</sub> (μM)	K <sub>i</sub> (μM)	N	IC <sub>50</sub> (μM)	K <sub>i</sub> (μM)	N	IC <sub>50</sub> (μM)	K <sub>i</sub> (μM)	N
L-97-1	> 100		3	> 100		3	67.33 ± 28.76		3
Bamiphylline	26.6 ± 7.9	12.92 ± 3.85	2	> 100		3	36.6 ± 4.00	17.55 ± 1.95	2
DPCPX				0.219 ± 0.065	0.12 ± 0.035	3			
CGS-21680	0.32 ± 0.215	0.158 ± 0.106	3						
CI-IB-MECA							0.19 nM	0.09 nM	1

**EXAMPLE 3**

15

A feline model of acute lung injury following endotoxin administration was employed to study the effects of the A<sub>1</sub> adenosine receptor antagonist, bamiphylline (BAM), or P<sub>2x</sub> antagonist, PPADS, on alveolar inflammatory cells, red blood cells, edema, and injury index in lungs after endotoxin treatment.

BAM was dissolved in 0.9% saline at 2 to 4 mg/ml and administered at 10 mg/kg/hr as a continuous intravenous infusion during and for 30 minutes to cats after the endotoxin infusion (Group II, n=5). PPADS was administered at 15 mg/kg as an intravenous bolus 30 minutes before administration of the endotoxin (Group III, n=5). In addition, a combination of PPADS (15 mg/kg, i.v. prior to endotoxin administration) and BAM (10 mg/kg/hr, continuous intravenous infusion 30 minutes prior to and throughout endotoxin until 1 hour post endotoxin) was administered (Group IV, n=5). *E. coli* endotoxin (Sigma Chemical Com., St. Louis, Mo.) was dissolved in 0.9% saline at 2.5 mg/ml. The endotoxin (15 mg/kg) was administered to treated groups and to a group of untreated cats (Group I, n=5) as a continuous intralobar infusion over 30 to 40 minutes into the left lower lobe. In control animals

- 5 (Group V, n=5), the lower left lobe was perfused for one hour only with blood drawn from the aorta. Two hours after completion of the endotoxin infusion, the cats received an overdose of pentobarbital (50 mg/kg) and the left lower lobe was perfusion fixed *in situ* and the lung specimens were analyzed as described in U.S. Patent No. 6,001,842 in Example 4. The results are shown below in Table 3.

10

**Table 3.**

Treatment groups	PMN <sup>1</sup>		Macro <sup>1</sup>		RBC <sup>1</sup>		Edematous alveoli %	Injured <sup>2</sup> alveoli %
	Alv %	#/alv	alv %	#/alv	Alv %	#/alv		
I Endotoxin (n=5)	25±9*	0.33±0.14*	26±12*	0.38±0.19*	50±3.2*	2.03±1.24*	22±17*	57±31*
II BAM + EN (n=5)	8±4	0.11±0.07	7±4	0.09±0.05	14±4†	0.56±0.51	5±3†	21±14†
III PPADS + EN (n=5)	9±4	0.10±0.04	8±3	0.10±0.04	6±3	0.13±0.09	1±1	7±3
IV BAM+PPADS + EN (n=5)	7±3	0.08±0.04	8±6	0.17±0.23	8±4	0.22±0.12	0.3±0.6	6±4
V Control (n=5)	6±3	0.06±0.04	6±3	0.09±0.08	7±2	0.11±0.05	0.3±0.5	5±4

Means and standard deviations: n = number of cats.

- <sup>1</sup>Alv(%) = percent alveoli containing two or more cells; #/alv = average number of cells per alveolus;
- <sup>2</sup>Average percent alveoli with two or more inflammatory cells or RBC, or edematous fluid; Group I: endotoxin (EN) treatment, 15 mg/kg i.v.; II: BAM, i.v., continuous infusion 30 min. prior to and throughout EN until 30 min. post EN; III: PPADS, i.v., 30 min. prior to EN; IV: combined PPADS and BAM treatment; V: control, 1 hour arterial perfusion only.
- \*Significantly different from all EN groups with A<sub>1</sub> adenosine receptor antagonist and P<sub>2x</sub> antagonist treatment (groups II, III and IV), and control; ANOVA and Bonferroni range test, at p ≤ 0.05; % data were arcsin transformed.
- †Group II given BAM only had higher numbers of alveoli containing RBC, edematous alveoli, and injured alveoli, compared with groups III and IV given PPADS, using Student's t-test for unpaired data at p ≤ 0.05.

#### EXAMPLE 4

- Hemodynamic measurements, including mean lobar arterial, femoral arterial, and left atrial pressures were obtained before endotoxin infusion (baseline), during endotoxin infusion and two hours following initiation of the endotoxin infusions. Data were analyzed and summarized in Table 4 below. These studies show that BAM and PPADS combined have a greater effect on endotoxin-induced hypotension (i.e., shock following intralobar administration of endotoxin) than either treatment alone.

35

5 **Table 4.**

Pressures	Group I	Group II	Group III	Group IV	Group V
Lobar Arterial	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)
<b>Baseline</b>	5.7±2.1	3.8±0.7	3.2±1.0	4.4±1.1	5.6±2.0
5' after endotoxin	5.7±1.4	6.0±1.6	5.9±1.2	6.0±0.6	
15' after endotoxin	6.3±1.9	5.2±1.1	5.6±0.7	5.3±0.6	
30' after endotoxin	6.3±2.0	3.8±0.2	4.4±0.8	4.2±0.5	
60' after endotoxin	5.4±1.6	4.2±0.5	3.6±1.2T	5.3±0.5	7.0±1.4
120' after endotoxin	7.0±2.1	5.7±1.5	4.6±2.2	5.1±1.2	
Femoral Arterial	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)
<b>Baseline</b>	131±10.4	147±11.5	139±4.9	137±11	131±2.4
5' after endotoxin	106±6.8	115±5.2*	123±8.5	121±8.4	
15' after endotoxin	105±3.5	107±3.7*	120±9.5	120±9.6	
30' after endotoxin	89±6.8*	103±2.5*	114±9.7	116±7.3	
60' after endotoxin	85±10.7*T	107±6.6*T	106±6.6*T	114±8.0T	134±7.0
120' after endotoxin	87±11.2*	111±7.3*	111±10.8*	120±7.6	
Left atrial	(n=5)	(n=5)	(n=5)	(n=4)	(n=2)
<b>Baseline</b>	0.6±0.4	1.1±0.8	0.9±0.6	1.3±1.0	1.5±1.5
5' after endotoxin	1.1±0.7	0.2±0.2	1.7±1.4	0.9±0.6	
15' after endotoxin	1.3±0.8	0.6±0.4	1.0±1.0	0.1±0.1	
30' after endotoxin	1.3±0.9	0.7±0.4	0.6±0.6	0	
60' after endotoxin	0.8±0.8	0.6±0.6	0.1±0.1	0	0.5±0.5
120' after endotoxin	0.5±0.3	2.0±1.5	0.2±0.2	0	

Data expressed as mean ± SEM; n = number of animals; Group I, endotoxin (15 mg/kg, i.a.); Group II, endotoxin (15 mg/kg, i.a.) + BAM continuous infusion (10 mg/kg/hr, IV) 30 min. before, during and after endotoxin; Group III, endotoxin (15 mg/kg, i.a.) + PPADS (15 mg/kg, IV) 30 minutes before endotoxin; Group IV, endotoxin (15 mg/kg, i.a.) + PPADS (15 mg/kg, IV) 30 minutes before + BAM 30 minutes before, during and after endotoxin; Group V, controls 1-h perfusion only.

\*Different compared with baseline within a group using Student's t-test with Bonferroni correction (p<0.05).

10

- 5 T Different compared with Group V at the same time with use of ANOVA with Bonferroni correction ( $p < 0.05$ ).

The foregoing is illustrative of the present invention, and is not to be construed  
10 as limiting thereof. The invention is defined by the following claims, with  
equivalents of the claims to be included therein.

That Which is Claimed is:

1. A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A<sub>1</sub> adenosine receptor antagonist or a P<sub>2x</sub> purinoceptor antagonist with (b) an at least one additional active agent effective to treat said purinoceptor-related disorder.
2. The method according to claim 1, wherein the purinoceptor-related disorder is an inflammatory disorder.
3. The method according to claim 1, wherein the purinoceptor-related disorder is selected from the group consisting of congestive heart failure, systemic hypertension, pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, anaphylactic shock, allergic rhinitis, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, allergic conditions, autoimmune disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, fibrosis, sclerosis, renal failure, adult respiratory distress syndrome (ARDS), Severe Acute Respiratory Syndrome (SARS), Acute Lung Injury (ALI), septicemia, substance abuse, drug dependence, and Parkinson's disease.
4. The method according to claim 1, wherein the purinoceptor related disorder is asthma.
5. The method according to claim 4, wherein the asthma is intrinsic asthma.
6. The method according to claim 4, wherein the asthma is extrinsic asthma.
7. The method according to claim 1, wherein the purinoceptor-related disorder is septicemia.

8. The method according to claim 1, wherein the purinoceptor-related disorder is an autoimmune disorder.

9. The method according to claim 1, wherein the purinoceptor-related disorder is coronary artery disease.

10. The method according to claim 1, wherein the at least one additional active agent effective to treat said purinoceptor-related disorder is selected from the group consisting of steroids, beta-2 agonists, xanthines, A<sub>1</sub> adenosine receptor antagonists, A<sub>2a</sub> adenosine receptor agonists, A<sub>2b</sub> adenosine receptor antagonists, A<sub>3</sub> adenosine receptor antagonists, P<sub>2y</sub> purinoceptor agonists, P<sub>2x</sub> purinoceptor antagonists, TNF alpha mAb, TNF alpha antagonists, selectin antagonists, beta-2 integrin blockers, interferon, disease modifying anti-rheumatic drugs (DMARDs), proteasome inhibitors, VAP-1 mAb, rNIF, immunomodulators, NHE inhibitors, monophosphoryl Lipid A (MPL A), mycobacterium, endotoxin, interferon-alpha, granulocyte colony stimulating factor (GCSF), granulocyte-macrophage colony stimulating factor (GMCSF), endotoxin antagonists, antifactor IX mAb, p38 MAPK inhibitor, lipid emulsion, re PAF acetylhydrolase, CD14 receptor antagonist, caspase inhibitors, protease inhibitors, nitric oxide scavengers, nitric oxide blockers, nitric oxide synthetase inhibitors, re tissue factor protein inhibitors (re TFPI), bactericidal permeabilizing increasing re (BPI) protein fragment, CpG DNA, Mycobacterium vaccae, lactobacillus, modified endotoxin – Lipid A, diuretics, vasodilators, anti-platelet agents, anticoagulants, nitrates, calcium channel blockers, beta receptor antagonists, antihypertensives, diuretics, antidepressants, appetite suppressants, mast cell stabilizers, anti-histamines, cetirizine, leukotriene receptor antagonists, anticytokines, phosphodiesterase enzyme inhibitors, 5-lipoxygenase inhibitors, platelet activating factor antagonists, thromboxane receptor antagonists, neurokinin receptor antagonists, central nervous system (CNS) stimulants, cognition enhancers, acetylcholinesterase inhibitors, acridine derivatives, complement receptor antagonists, cyclosporin, endothelin receptor antagonists, angiotensin enzyme converting (ACE) inhibitors, antisense oligonucleotides, anti-IgE, insulin, oral hypoglycemics, smooth muscle relaxants, antibiotics, antiviral agents, antifungal agents, anti-inflammatory

agents, cancer therapies, narcotics, antitussive agents, surfactants, and combinations thereof.

11. The method according to claim 1, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of fluticasone, salmeterol, theophylline, and combinations, thereof.

12. The method according to claim 1, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of A<sub>1</sub> adenosine receptor antagonists, A<sub>2a</sub> adenosine receptor agonists, A<sub>2b</sub> adenosine receptor antagonists, A<sub>3</sub> adenosine receptor antagonists, P<sub>2y</sub> purinoceptor agonists, P<sub>2x</sub> purinoceptor antagonists, and combinations thereof.

13. The method according to claim 1, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is an at least one bronchodilating agent.

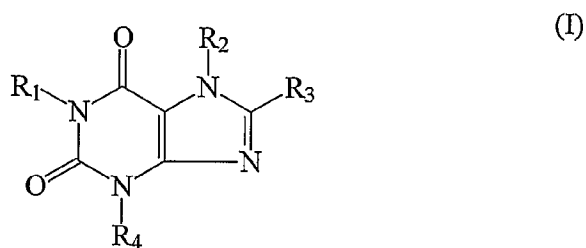
14. The method according to claim 1, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is an at least one anti-inflammatory agent.

15. The method according to claim 1, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is at least one agent useful for the prevention or treatment of coronary artery disease.

16. The method according to claim 1, wherein the administering step comprises inhalation therapy.

17. The method according to claim 1, wherein the administering step comprises oral administration.

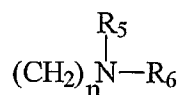
18. The method according to claim 1, wherein the A<sub>1</sub> adenosine receptor antagonist comprising a compound of Formula I:



wherein

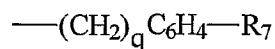
$R_1$  is selected from the group consisting of  $C_1$ - $C_8$  alkyl;

$R_2$  is of the formula:



wherein  $n$  is an integer ranging from 1 to 8;  $R_5$  is H or  $CH_3(CH_2)_p$ , wherein  $p$  is an integer ranging from 1 to 7; and  $R_6$  is H or  $(CH_2)_mOH$ , wherein  $m$  is an integer ranging from 1 to 8;

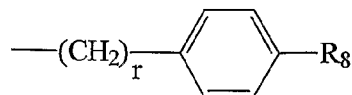
$R_3$  is of the formula:



and

wherein  $q$  is an integer ranging from 1 to 8; and wherein  $R_7$  is selected from the group consisting of H,  $NH_2$ ,  $R_9COOH$ , wherein  $R_9$  is an alkylene or alkenylene group having 1 to 8 carbon atoms, and  $(CH_2)_tOH$ , wherein  $t$  is an integer ranging from 1 to 8; and

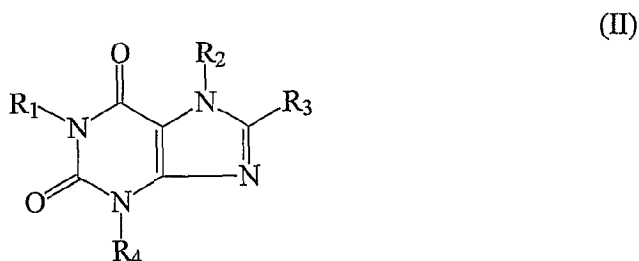
$R_4$  is of the formula:



wherein  $R_8$  is selected from the group consisting of H;  $NH_2$ ;  $(CH_2)_sOH$ , wherein  $s$  is an integer ranging from 1 to 8; and  $R_{10}COOH$ , wherein  $R_{10}$  is an alkylene

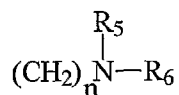
or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8, or a pharmaceutically acceptable salt thereof, or a P<sub>2x</sub> purinoceptor antagonist or a pharmaceutically acceptable salt thereof.

19. The method according to claim 18, wherein the A<sub>1</sub> adenosine receptor antagonist comprises a compound of Formula II:



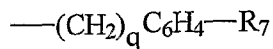
wherein R<sub>1</sub> is C<sub>3</sub> alkyl;

R<sub>2</sub> is of the formula:



wherein n is 2; R<sub>5</sub> is CH<sub>3</sub>(CH<sub>2</sub>)<sub>p</sub>, wherein p is 1; R<sub>6</sub> is (CH<sub>2</sub>)<sub>m</sub>OH, wherein m is 2;

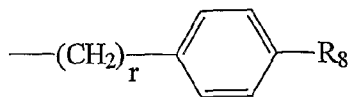
R<sub>3</sub> is of the formula:



and

wherein q is 1; R<sub>7</sub> is H; and

R<sub>4</sub> is of the formula:



wherein R<sub>8</sub> is NH<sub>2</sub>; and r is 2; or

a pharmaceutically acceptable salt thereof.

20. The method according to claim 18, wherein the purinoceptor-related disorder is an inflammatory disorder.

21. The method according to claim 18, wherein the purinoceptor-related disorder is selected from the group consisting of congestive heart failure, systemic hypertension, pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, anaphylactic shock, allergic rhinitis, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, allergic conditions, autoimmune disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, fibrosis, sclerosis, renal failure, adult respiratory distress syndrome (ARDS), Severe Acute Respiratory Syndrome (SARS), Acute Lung Injury (ALI), septicemia, substance abuse, drug dependence, and Parkinson's disease.

22. The method according to claim 18, wherein the purinoceptor-related disorder is asthma.

23. The method according to claim 22, wherein the asthma is intrinsic asthma.

24. The method according to claim 22, wherein the asthma is extrinsic.

25. The method according to claim 18, wherein the purinoceptor-related disorder is septicemia.

26. The method according to claim 18, wherein the purinoceptor-related disorder is an autoimmune disorder.

27. The method according to claim 18, wherein the purinoceptor-related disorder is coronary artery disease.

28. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of steroids, beta-2 agonists, xanthines, A<sub>1</sub> adenosine receptor

antagonists, A<sub>2a</sub> adenosine receptor agonists, A<sub>2b</sub> adenosine receptor antagonists, A<sub>3</sub> adenosine receptor antagonists, P<sub>2y</sub> purinoceptor agonists, P<sub>2x</sub> purinoceptor antagonists, TNF alpha mAb, TNF alpha antagonists, selectin antagonists, beta-2 integrin blockers, interferon, disease modifying anti-rheumatic drugs (DMARDs), proteasome inhibitors, VAP-1 mAb, rNIF, immunomodulators, NHE inhibitors, monophosphoryl Lipid A (MPL A), mycobacterium, endotoxin, interferon-alpha, granulocyte colony stimulating factor (GCSF), granulocyte-macrophage colony stimulating factor (GMCSF), endotoxin antagonists, antifactor IX mAb, p38 MAPK inhibitor, lipid emulsion, re PAF acetylhydrolase, CD14 receptor antagonist, caspase inhibitors, protease inhibitors, nitric oxide scavengers, nitric oxide blockers, nitric oxide synthetase inhibitors, re tissue factor protein inhibitors (re TFPI), bactericidal permeabilizing increasing re (BPI) protein fragment, CpG DNA, Mycobacterium vaccae, lactobacillus, modified endotoxin – Lipid A, diuretics, vasodilators, anti-platelet agents, anticoagulants, nitrates, calcium channel blockers, beta receptor antagonists, antihypertensives, diuretics, antidepressants, appetite suppressants, mast cell stabilizers, anti-histamines, cetirizine, leukotriene receptor antagonists, anticytokines, phosphodiesterase enzyme inhibitors, 5-lipoxygenase inhibitors, platelet activating factor antagonists, thromboxane receptor antagonists, neurokinin receptor antagonists, central nervous system (CNS) stimulants, cognition enhancers, acetylcholinesterase inhibitors, acridine derivatives, complement receptor antagonists, cyclosporin, endothelin receptor antagonists, angiotensin enzyme converting (ACE) inhibitors, antisense oligonucleotides, anti-IgE, insulin, oral hypoglycemics, smooth muscle relaxants, antibiotics, antiviral agents, antifungal agents, anti-inflammatory agents, cancer therapies, narcotics, antitussive agents, surfactants, and combinations thereof.

29. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of fluticasone, salmeterol, theophylline, and combinations, thereof.

30. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of A<sub>1</sub> adenosine receptor antagonists, A<sub>2a</sub> adenosine receptor

agonists, A<sub>2b</sub> adenosine receptor antagonists, A<sub>3</sub> adenosine receptor antagonists, P<sub>2y</sub> purinoceptor agonists, P<sub>2x</sub> purinoceptor antagonists, and combinations thereof.

31. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is an at least one bronchodilating agent.

32. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is an at least one anti-inflammatory agent.

33. The method according to claim 18, wherein the at least one additional active agent effective to treat the purinoceptor-related disorder is an agent useful for the prevention or treatment of coronary artery disease.

34. The method according to claim 18, wherein the purinoceptor-related disorder is Alzheimer's disease and the at least one additional active agent effective to treat the purinoceptor-related disorder is selected from the group consisting of cognition enhancers and anti-inflammatory agents, and combinations thereof.

35. The method according to claim 18, wherein the administering step comprises inhalation therapy.

36. The method according to claim 18, wherein the administering step comprises oral administration.

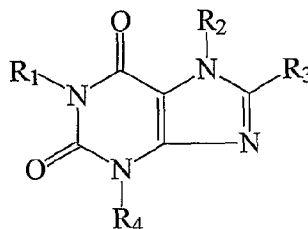
37. A method of treating coronary artery disease comprising administering an A<sub>1</sub> adenosine receptor antagonist or a P<sub>2x</sub> purinoceptor antagonist in combination with at least one additional active agent selected from the group consisting of nitrates, calcium channel blockers, beta blockers, anticoagulants, and combinations thereof.

38. A method of treating asthma comprising administering an A<sub>1</sub> adenosine receptor antagonist or a P<sub>2x</sub> purinoceptor antagonist in combination with at least one additional active agent selected from the group consisting of A<sub>1</sub> adenosine receptor antagonists, A<sub>2a</sub> adenosine receptor agonists, A<sub>2b</sub> adenosine receptor antagonists, A<sub>3</sub> adenosine receptor antagonists, P<sub>2y</sub> purinoceptor agonists, P<sub>2x</sub> purinoceptor antagonists, leukotriene receptor antagonists, anticytokines, phosphodiesterase enzyme inhibitors, histamine antagonists, and combinations thereof.

39. A method of treating autoimmune disorders comprising administering an A<sub>1</sub> adenosine receptor antagonist or a P<sub>2x</sub> purinoceptor antagonist in combination with at least one additional active agent selected from the group consisting of anti-inflammatory agents, antibiotic agents, antiviral agents, and P<sub>2y</sub> purinoceptor agonists.

40. The method according to claim 37, 38, or 39, wherein the A<sub>1</sub> adenosine receptor antagonist comprises a compound of Formula I:

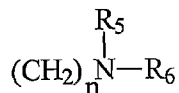
(I)



wherein

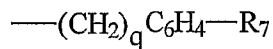
R<sub>1</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>8</sub> alkyl;

R<sub>2</sub> is of the formula:



wherein n is an integer ranging from 1 to 8;  $R_5$  is H or  $\text{CH}_3(\text{CH}_2)_p$ , wherein p is an integer ranging from 1 to 7; and  $R_6$  is H or  $(\text{CH}_2)_m\text{OH}$ , wherein m is an integer ranging from 1 to 8;

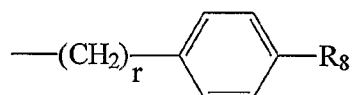
$R_3$  is of the formula:



and

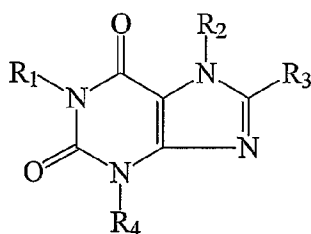
wherein q is an integer ranging from 1 to 8; and wherein  $R_7$  is selected from the group consisting of H,  $\text{NH}_2$ ,  $\text{R}_9\text{COOH}$ , wherein  $R_9$  is an alkylene or alkenylene group having 1 to 8 carbon atoms, and  $(\text{CH}_2)_t\text{OH}$ , wherein t is an integer ranging from 1 to 8; and

$R_4$  is of the formula:



wherein  $R_8$  is selected from the group consisting of H;  $\text{NH}_2$ ;  $(\text{CH}_2)_s\text{OH}$ , wherein s is an integer ranging from 1 to 8; and  $\text{R}_{10}\text{COOH}$ , wherein  $\text{R}_{10}$  is an alkylene or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8, or a pharmaceutically acceptable salt thereof.

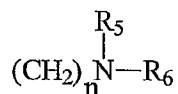
41. The method according to claim 40, wherein the  $A_1$  adenosine receptor antagonist comprises a compound of Formula II:



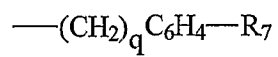
(II)

wherein  $R_1$  is  $\text{C}_3$  alkyl;

$R_2$  is of the formula:

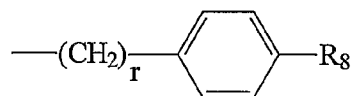


wherein n is 2; R<sub>5</sub> is CH<sub>3</sub>(CH<sub>2</sub>)<sub>p</sub>, wherein p is 1; R<sub>6</sub> is (CH<sub>2</sub>)<sub>m</sub>OH, wherein m is 2;  
R<sub>3</sub> is of the formula:



and

wherein q is 1; R<sub>7</sub> is H; and  
R<sub>4</sub> is of the formula:



wherein R<sub>8</sub> is NH<sub>2</sub>; and r is 2; or  
a pharmaceutically acceptable salt thereof.